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L1 3046 SULFISOXAZOLE

=> s l1 and conjugate

L2 37 L1 AND CONJUGATE

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L3 19 DUP REMOVE L2 (18 DUPLICATES REMOVED)

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L3 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2001 ACS
2001:380414 Document No. 134:371812 Targeted bifunctional molecules and therapies based thereon. Briesewitz, Roger; Crabtree, Gerald R.; Wandless, Thomas (Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 2001035978 A1 20010525, 31 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31702 20001117. PRIORITY: US 1999-PV166580 19991119.

AB Targeted bifunctional mols. and methods for their use are provided. The subject targeted bifunctional mols. are **conjugates** of a drug moiety and a targeting moiety, where these two moieties are optionally joined by a linking group. The bifunctional mols. are further characterized in that they exhibit a modulated biodistribution upon administration to a host as compared to a free drug control. The subject targeted bifunctional mols. find use in a variety of therapeutic applications. For example, a bifunctional mol. consisting of a drug moiety covalently joined to **sulfisoxazole** which is extensively bound by albumin, via an inert linking group is formed. When this bifunctional mol. enters the human circulation, it is bound by albumin which keeps the drug of interest in the extracellular environment.

L3 ANSWER 2 OF 19 MEDLINE DUPLICATE 1
2001137492 Document Number: 21017764. PubMed ID: 11144704. treatment and prevention of otitis media. Erramouspe J; Heyneman C A. (College of Pharmacy, Idaho State University, Pocatello 83209-8333, USA..

johnerra@otc.isu.edu) . ANNALS OF PHARMACOTHERAPY, (2000 Dec) 34 (12) 1452-68. Ref: 129. Journal code: BBX; 9203131. ISSN: 1060-0280. Pub. country: United States. Language: English.

AB OBJECTIVE: To review and summarize recent advances in the treatment and prevention of otitis media (OM). DATA SOURCES: A MEDLINE search (1996-March 2000) was performed to identify relevant primary and review articles. References from these articles were also reviewed if deemed important. STUDY SELECTION AND DATA EXTRACTION: English-language primary and review articles focusing on the treatment and prevention of acute otitis media (AOM) were included. Studies focusing exclusively on OM with effusion or serous OM and chronic suppurative OM were excluded. Information regarding prevention and drug therapy was reviewed, with an emphasis placed on advances made in the last two years. DATA SYNTHESIS: Recently, an expert panel of the Centers for Disease Control and Prevention recommended use of only three of 16 systemic antibiotics approved by the Food and Drug Administration for treatment of AOM: amoxicillin, cefuroxime axetil, and ceftriaxone. Controversy exists over the importance of key selection factors used by the expert panel in determining which antibiotics to recommend in a two-step treatment algorithm, that is, in vitro data, pharmacodynamic profiles, and necessity for coverage of drug-resistant Streptococcus pneumoniae at all steps of empiric treatment. Additional antibiotic and patient selection factors useful for individualizing therapy include clinical efficacy, adverse effects, frequency and duration of administration, taste, cost, comorbid infections, and ramifications should bacterial resistance develop to the chosen antibiotic. Presumed or past patient/caregiver adherence (especially when antibiotic failure has occurred) is also paramount in selecting antibiotic therapy. A three-step treatment algorithm for refractory AOM that employs amoxicillin, trimethoprim/sulfamethoxazole (TMP/SMX), or high-dose amoxicillin/clavulanate (depending on the prior dose of and adherence to amoxicillin therapy), and ceftriaxone or tympanocentesis at steps 1, 2, and 3, respectively, appears rational and cost-effective. The recent upsurge in antimicrobial resistance is highlighted, and recommendations are presented for the treatment of AOM and prevention of recurrent otitis media (rAOM). CONCLUSIONS: Amoxicillin remains the antibiotic of choice for initial empiric treatment of AOM, although the traditional dosage should be increased in patients at risk for drug-resistant S. pneumoniae. In cases refractory to high-dose amoxicillin, TMP/SMX should be prescribed if adherence to prior therapy seemed good or complete, or high-dose amoxicillin/clavulanate if adherence was incomplete or questionable. Ceftriaxone should be reserved as third-line treatment. The increasing prevalence of drug-resistant S. pneumoniae emphasizes the importance of alternative medical approaches for the prevention of OM, as well as judicious antibiotic use in established cases. Removal of modifiable risk factors should be first-line therapy for prevention of rAOM. We support the use of **conjugate** pneumococcal vaccine per guidelines for prevention of rAOM from the Advisory Committee on Immunization Practice of the Centers for Disease Control and Prevention, with consideration given to influenza vaccine for cases of rAOM that historically worsen during the flu season. **Sulfisoxazole** prophylaxis should be reserved for children who are immunocompromised, have concurrent disease states exacerbated by AOM, or meet the criteria of rAOM despite **conjugate** pneumococcal and influenza vaccination. Therapy should be intermittent, beginning at the first sign of an upper respiratory infection, and should continue for 10 days. The invasive nature and risks of anesthesia relegate myringotomy, tympanostomy tubes, and adenoidectomy to last-line therapies for rAOM.

L3 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2

2000:184729 Document No.: PREV200000184729. Sulphonamide antibodies: From specific polyclonals to generic monoclonals. Haasnoot, Willem (1); Cazemier, Geert; Du Pre, Jolanda; Kemmers-Voncken, Anniek; Bienenmann-Ploum, Monique; Verheijen, Ron. (1) State Institute for Quality Control of Agricultural Products (RIKILT), Bornsesteeg 45, 6708 PD, Wageningen Netherlands. Food and Agricultural Immunology, (March, 2000) Vol. 12, No. 1, pp. 15-30. ISSN: 0954-0105. Language: English. Summary Language: English.

AB Polyclonal antibodies (PAbs) against eight different sulphonamides were raised in rabbits. The aromatic amino group, common to all sulphonamides, was used for linking the different sulphonamides to the carrier proteins (bovine serum albumin (BSA) and keyhole limpet haemocyanin (KLH)) and enzyme (horseradish peroxidase (HRP)), using different coupling procedures. The competitive direct ELISAs (cdELISAs) developed with these antisera and HRP-**conjugates** showed high sensitivity (0.2-8.0 ng ml-1 at 50% inhibition) and high specificity. The performances of these antibodies were compared with PAbs raised in mice against two sulphonamide derivatives (N1-(4-(carboxymethyl)-2-thiazolyl)sulphanilamide (TS) and N1-(4-methyl-5-(2-(4-carboxyethyl-1-hydroxyphenyl))-azo-2-pyridyl)sulphanilamide (PS)) linked to proteins (BSA and KLH) in such a way that the common aromatic amino group was distal to the protein. In competitive indirect ELISAs (ciELISAs), these PAbs recognized several structurally different sulphonamides. The PAbs from mice immunized with TS-BSA reacted with sulphonamides containing thiazolyl, thiadiazolyl, pyridazinyl and isoxazolyl groups. The PAbs from mice immunized with PS-KLH reacted with sulphonamides containing pyrimidinyl, pyridazinyl, quinoxalinyl and pyridinyl groups. The spleen cells of the mice were fused with myeloma cells to obtain monoclonal antibodies (MAbs) producing hybridomas. So far, with only one of the mice (immunized with TS-BSA), this resulted in four different MAbs which recognized several sulphonamides. By use of the best MAbs (27G3A9B10 and 4E10B12B6E12) and an optimized ciELISA protocol, eight structurally different sulphonamides showed 50% inhibition at concentrations less than 100 ng ml-1 or 5 ng/well. However, other relevant sulphonamides (such as sulphadimidine, sulphatroxazole and sulphachloropyrazine) were detected at a high level only.

L3 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2001 ACS

1998:300862 Document No. 129:4868 Preparation of targetable diagnostic and therapeutic gas-contg. or gas-generating ultrasound contrast agents. Klaveness, Jo; Rongved, Pal; Hogset, Anders; Tolleshaug, Helge; Godal, Aslak; et al. (Marsden, John Christopher, UK; Nycomed Imaging AS; Klaveness, Jo; Rongved, Pal). PCT Int. Appl. WO 9818495 A2 19980507, 108 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-GB2955 19971028. PRIORITY: GB 1996-22365 19961028; GB 1996-22367 19961028; GB 1996-22366 19961028; GB 1997-699 19970115; GB 1997-8265 19970424; GB 1997-11842 19970606; GB 1997-11845 19970606; US 1997-49267 19970606; US 1997-49264 19970606; US 1997-49265 19970606.

AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, comprising a suspension in an aq. carrier liq. of a reporter comprising gas-contg. or gas-generated material, said reporter being conjugated to one or more non-proteinaceous, non-peptide and non-polysaccharide vectors. Thus, a mixt. of phosphatidylserine,

phosphatidylcholine, and biotinamidocaproate-PEG3400-L-Ala-cholesterol (prepn. given) was dispersed in 5% propylene glycol-water, flushed with perfluorobutane, and sonicated to give gas-filled encapsulated microbubbles.

L3 ANSWER 5 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
1998360277 EMBASE [Haemophilus influenzae infections]. H INFLUENZAE INFEKSIYONLARI. Torun M.M.; Vural S.. Dr. M.M. Torun, Instanbul Universitesi, Tip Fakultesi, Mikrobiyoliji Klinik Mikrobiyol. AD, Istanbul, Turkey. SENDROM 10/9 (38-44) 1998.
Refs: 29.
ISSN: 1016-5134. CODEN: SENDEY. Pub. Country: Turkey. Language: Turkish. Summary Language: English.
AB Haemophilus influenzae was first described in 1892 by Pfeiffer, who found it in sputa of several patients with influenza. Pitman described the six capsular serotypes of H influenza in 1931. Two contrasting patterns of H influenzae diseases can be identified: The first and the most serious in its consequences is invasive infection such as meningitis, septic arthritis, epigliottis and cellulitis in which bacteremia is a prominent feature; These infections are usually caused by the type b strains and occur in young children. The second category includes less serious but numerically more common infections that occur as a result of contagious spread of H influenzae within the respiratory tract (e.g; otitis media, sinusitis, conjunctivitis and bronchopneumoniae). These later infections are usually caused by unencapsuled strains. Meningitis due to H influenzae type b can be treated initially with one of two equally effective regimens: ampicillin plus chloramphenicol or one of the new cephalosporins such as ceftriaxone or cefotaxime. Invasive infections other than meningitis are treated with the same antimicrobial agents. Many infections caused by nontypable strains of H influenzae can be treated with oral antimicrobial agents. Ampicillin- resistant strains are sensitive to sulfonamides, trimethoprim- sulfamethoxazole, erythromycin- **sulfisoxazole**, cefaclor and amoxicillin- clavulanic acid. There are four **conjugate** vaccines for the prevention of H influenzae type b diseases: PRP-D, HbOC, PRP-OMPG and PRP-T. Currently no vaccines are available for prevention of disease caused by nontypable H influenzae.

L3 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2001 ACS
1997:530506 Document No. 127:229243 Patients with delayed-onset sulfonamide hypersensitivity reactions have antibodies recognizing endoplasmic reticulum luminal proteins. Cribb, Alastair E.; Pohl, Lance R.; Spielberg, Stephen P.; Leeder, J. Steven (Merck Research Laboratories, West Point, PA, USA). J. Pharmacol. Exp. Ther., 282(2), 1064-1071 (English) 1997. CODEN: JPETAB. ISSN: 0022-3565. Publisher: Williams & Wilkins.
AB Sulfonamide antimicrobials cause a delayed-onset, hypersensitivity-type syndrome characterized by fever, skin rash and multiorgan toxicity occurring 7 to 14 days after initiation of therapy. The pathogenesis is believed to be immune-mediated. We investigated whether patients with delayed-onset sulfonamide hypersensitivity reactions had antibodies recognizing hapten-microsomal protein **conjugates** and/or native microsomal proteins. By immunoblotting using rat liver as a source of microsomal protein, 17 of 21 patients had antibodies recognizing one or more of three native endoplasmic reticulum proteins of 55 kDa (14 of 21 patients), 80 kDa (4 of 21 patients) or 96 kDa (3 of 21 patients) in size on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. No control subjects (n = 11) and only 1 of 18 patients with adverse events not consistent with sulfonamide hypersensitivity reactions had antibodies against these microsomal proteins under the conditions used. Only 1 patient had antibodies that recognized the sulfonamide hapten,

sulfamethoxazole. The 55-kDa protein was identified as protein disulfide isomerase. The 80-kDa protein was identified as grp78. The 96-kDa protein was not identified. Delayed-onset sulfonamide hypersensitivity reactions are therefore primarily assocd. with antibodies recognizing specific protein epitopes and not anti-drug antibodies.

L3 ANSWER 7 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
94155057 EMBASE Document No.: 1994155057. Preventing otitis media. Giebink G.S.. Dept of Pediatrics, Box 483 UMHC, 420 Delaware St SE,Minneapolis, MN
55455, United States. Annals of Otology, Rhinology and Laryngology 103/5 II (20-23) 1994.
ISSN: 0003-4894. CODEN: AORHA2. Pub. Country: United States. Language: English. Summary Language: English.
AB Recurrent acute otitis media (AOM) is an extremely prevalent disease in young children. Epidemiologic associations suggest that primary prevention
or reduction of AOM frequency may be achieved with breast-feeding during infancy, elimination of household tobacco smoking, and use of small rather
than large day-care arrangements for infants and toddlers. Secondary antimicrobial prophylaxis with amoxicillin or **sulfisoxazole** reduces the frequency of recurrent AOM by about 50%, but it does not appear to reduce the duration of otitis media with effusion (OME). Tympanostomy tube insertion is not as effective as amoxicillin in reducing
AOM frequency in children without OME. Adenoidectomy appears to be warranted for children who develop recurrent AOM after extrusion of tubes.
Vaccines against the common bacteria and viruses causing AOM hold the greatest promise of preventing AOM and blocking the sequence of pathologic
events leading to chronic OME and middle ear sequelae. The greatest progress has been made recently with pneumococcal protein **conjugate** vaccines, and clinical testing is in progress.

L3 ANSWER 8 OF 19 MEDLINE
94234646 Document Number: 94234646. PubMed ID: 8179264. Preventing otitis
media. Giebink G S. (Otitis Media Research Center, University of Minnesota
School of Medicine, Minneapolis.) ANNALS OF OTOLOGY, RHINOLOGY, AND LARYNGOLOGY. SUPPLEMENT, (1994 May) 163 20-3. Ref: 17. Journal code: 5Q3;
1256156. ISSN: 0096-8056. Pub. country: United States. Language: English.
AB Recurrent acute otitis media (AOM) is an extremely prevalent disease in young children. Epidemiologic associations suggest that primary prevention
or reduction of AOM frequency may be achieved with breast-feeding during infancy, elimination of household tobacco smoking, and use of small rather
than large day-care arrangements for infants and toddlers. Secondary antimicrobial prophylaxis with amoxicillin or **sulfisoxazole** reduces the frequency of recurrent AOM by about 50%, but it does not appear to reduce the duration of otitis media with effusion (OME). Tympanostomy tube insertion is not as effective as amoxicillin in reducing
AOM frequency in children without OME. Adenoidectomy appears to be warranted for children who develop recurrent AOM after extrusion of tubes.
Vaccines against the common bacteria and viruses causing AOM hold the greatest promise of preventing AOM and blocking the sequence of pathologic
events leading to chronic OME and middle ear sequelae. The greatest

progress has been made recently with pneumococcal protein **conjugate** vaccines, and clinical testing is in progress.

L3 ANSWER 9 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
91245849 EMBASE Document No.: 1991245849. Prevention of acute otitis media.
Klein J.O.. Division of Pediatric Infectious Diseases, Boston University School of Medicine, Boston City Hospital, Boston, MA 02118, United States.
Seminars in Hearing 12/2 (140-145) 1991.
ISSN: 0734-0451. CODEN: SEMHE7. Pub. Country: United States. Language: English. Summary Language: English.
AB 1. Otitis media is a disease of early infancy. Techniques for prevention of severe and recurrent disease must be implemented during the first years of life. 2. Infants at increased risk of acute otitis media are male, have a sibling history of recurrent acute otitis media, suffer early occurrence of otitis media, are not breast fed, and attend large group day care. Physicians should aggressively manage the child with these risk factors. Breastfeeding should be promoted. Children should be placed in daycare with few rather than many other attendees. 3. Prophylactic use of antimicrobial agents is highly effective in prevention of symptomatic episodes of recurrent acute otitis media. A modified dosage schedule of **sulfisoxazole** or amoxicillin may be used for up to 6 months during the months of increased infections of the respiratory tract. The incidence of resistance among respiratory bacteria and side effects and toxicity of the antibiotics has been low and is not a deterrent to chemoprophylaxis. 4. Vaccines for prevention of otitis media are in investigational stages. **Conjugate** polysaccharide pneumococcal vaccines show promise of preventing type-specific infections. Vaccines for nontypable H. influenzae and for respiratory viruses are in early stages of development. 5. Adenoidectomy alone or in combination with tonsillectomy and placement of ventilating tubes is believed to be effective for selected children with recurrent otitis media, although documentation of the benefit of these procedures is lacking.

L3 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2001 ACS
1988:431538 Document No. 109:31538 Intestinal absorption of drugs in rats with glycerol-induced acute renal failure. Kimura, Toshikiro; Kobayashi, Akira; Kobayashi, Miyoko; Numata, Kanae; Kawai, Yukichi; Kurosaki, Yuji; Nakayama, Taiji; Mori, Masaharu; Awai, Michiyasu (Fac. Pharm. Sci., Okayama Univ., Okayama, 700, Japan). Chem. Pharm. Bull., 36(5), 1847-56 (English) 1988. CODEN: CPBTAL. ISSN: 0009-2363.
AB The intestinal absorption of drugs was investigated in rats with glycerol-induced renal failure by an in situ loop method. Drugs examd. were poorly-absorbable drugs (sulfanilic acid, procainamide ethobromide, cefazolin and sulfaguanidine), well-absorbable drugs (**sulfisoxazole**, quinine, salicylic acid, and imipramine), actively-transported drugs (cefadroxil and cyclacillin) and water-sol., high-mol.-wt. compds. (polyethylene glycol (PEG) 1000, PEG 1500 and fluorescein isothiocyanate-conjugated dextran with a mol. wt. of 4000). The absorption of all the low-mol.-wt. drugs was increased in the renal failure group, regardless of the absorption characteristics. Enhancement of membrane permeability was also obsd. by an in vitro cannulated everted sac method. The investigation of membrane permeability to high-mol.-wt. compds. PEG and 1500 showed that the enhancement of membrane permeability in the renal failure state was limited to mols. whose mol. wts. were lower than about 1000. Furthermore, the enhancement of membrane permeability was seen in the brush border membrane vesicles prepd. from the small intestine of rats with renal failure, although lipid fluidity, as assessed

by steady-state fluorescence polarization techniques using 1,6-diphenyl-1,3,5-hexatriene as a probe was not changed in brush border membranes of the diseased rat. On the other hand, a redn. of thickness of the unstirred water adjacent to the membrane was obsd. Examn. by transmission electron microscopy revealed blebs at the tip of microvilli and the thickness of the glycocalyx was reduced. Possible mechanism of the increase in drug absorption are discussed sep. for poorly-absorbable and well-absorbable drugs.

L3 ANSWER 11 OF 19 MEDLINE DUPLICATE 4
89049006 Document Number: 89049006. PubMed ID: 3190184. In vitro displacement of bilirubin by antibiotics and 2-hydroxybenzoylglycine in newborns. Wadsworth S J; Suh B. (Section of Infectious Diseases, Temple University Health Sciences Center, Philadelphia, Pennsylvania 19140.) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1988 Oct) 32 (10) 1571-5. Journal code: 6HK; 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Hyperbilirubinemia is frequently observed in neonates, and serious neurological complications such as kernicterus can be precipitated when the concentration of unconjugated bilirubin is abnormally increased. The administration of drugs which bind to albumin and compete with bilirubin can increase the possibility of such a complication. To test the bilirubin-displacing activity of pharmacological agents that are used with newborns, 52 antimicrobial agents were investigated in vitro. A glycine **conjugate** of salicylate, 2-hydroxybenzoylglycine, which is known to be present at elevated levels in newborns and has a potent bilirubin-displacing property, was used as a positive control agent. Pooled cord serum was used as a source of hyperbilirubinemic serum. A centrifugal ultrafiltration method with semipermeable cones was employed to determine the effects of potential bilirubin-displacing agents on the levels of total bilirubin. 2-Hydroxybenzoylglycine was demonstrated to be the most potent bilirubin-displacing agent. Antibiotics could be classified into four groups: high-level displacers (**sulfisoxazole**, sulfamethoxazole, dicloxacillin, cefoperazone, and ceftriaxone), intermediate-level displacers (moxalactam, nafcillin, and 14 others), low-level displacers (aztreonam, carbenicillin, and 11 others), and nondisplacers (mezlocillin, cefuroxime, kanamycin, and 15 others). It is concluded that the ultrafiltration method is a rapid and readily reproducible for the determination of bilirubin displacement and that antibiotics with a tendency to displace bilirubin should be avoided in jaundiced newborns whenever appropriate alternatives are available.

L3 ANSWER 12 OF 19 MEDLINE DUPLICATE 5
84159529 Document Number: 84159529. PubMed ID: 6706125. Pharmacokinetics of **sulfisoxazole** in young and elderly subjects. Boisvert A; Barbeau G; Belanger P M. GERONTOLOGY, (1984) 30 (2) 125-31. Journal code: FPB; 7601655. ISSN: 0304-324X. Pub. country: Switzerland. Language: English.

AB The pharmacokinetics of **sulfisoxazole** was studied in 6 elderly (age 63-75 years) and 7 young (age 22-37 years) healthy nonsmoking volunteers following the oral administration of 2 g of Gantrisin. The plasma levels of **sulfisoxazole** obtained in the postabsorption phase were higher in the elderly subjects. There was no significant variation between the two groups of volunteers in the absorption rate constant, Cmax, bioavailability, the fraction of the dose of **sulfisoxazole** excreted unchanged, the area under the plasma curve of the N4-acetyl **conjugate** formed, and in the apparent volume of distribution of the drug. The tmax value and plasma half-life of **sulfisoxazole** were significantly longer, and the total body and renal clearances of the drug decreased in the elderly subjects. Diminished

renal function as estimated by the creatinine clearance and urinary flow may explain the slower elimination of **sulfisoxazole** in the elderly subjects. Therefore, advancing age should be considered as a factor in the adjustment of **sulfisoxazole** dosage.

L3 ANSWER 13 OF 19 MEDLINE DUPLICATE 6
77143547 Document Number: 77143547. PubMed ID: 845802. GI drug absorption
in rats exposed to cobalt-60 gamma-radiation I: Extent of absorption. Brady M E; Hayton W L. JOURNAL OF PHARMACEUTICAL SCIENCES, (1977 Mar) 66 (3) 361-5. Journal code: JO7; 2985195R. ISSN: 0022-3549. Pub. country: United States. Language: English.
AB The extent of absorption of sulfanilamide, bretylium tosylate, **sulfisoxazole** acetyl, and riboflavin was determined in rats exposed to 850 rad of cobalt-60 gamma-radiation of sham irradiated. The drug were administered orally at 1 or 5 days postirradiation, and the amount of drug excreted in the urine was used as the measure of absorption. Following intravenous drug administration, there was no difference between irradiated and control animals in the amount of drug excreted in the urine. At 1 day postirradiation, the absorption of sulfanilamide and bretylium was not affected by radiation; the absorption of **sulfisoxazole** acetyl and riboflavin was increased. The fraction of sulfanilamide excreted in the urine as N4-**conjugate** was increased at 1 day postirradiation. At 5 days postirradiation, there was no detectable difference between irradiated and control animals in the extent of drug absorption. The effects of radiation on the extent of absorption of orally administered drugs were most pronounced immediately following irradiation. Irradiation apparently does not affect the absorption of drugs that are normally well absorbed or poorly absorbed due to slow transport across the GI mucosa. Following irradiation, there may be an increase in the extent of absorption of drugs that are poorly absorbed due to low aqueous solubility or that are absorbed by a saturable transport mechanism.

L3 ANSWER 14 OF 19 MEDLINE DUPLICATE 7
76171356 Document Number: 76171356. PubMed ID: 1263077. Saturable first-pass metabolism of **sulfisoxazole** N1-acetyl in rats. Bloedow D C; Hayton W L. JOURNAL OF PHARMACEUTICAL SCIENCES, (1976 Mar) 65 (3) 334-8. Journal code: JO7; 2985195R. ISSN: 0022-3549. Pub. country: United States. Language: English.
AB Saturable metabolism of **sulfisoxazole** N1-acetyl in the rat during the initial pass of the drug from the intestinal lumen through the liver following oral administration of the drug (saturable first-pass metabolism) was investigated. The fraction of the total amount of drug recovered from the urine as the N4-**conjugate** fraction was apparent following the intravenous administration of **sulfisoxazole** acetyl or the oral administration of **sulfisoxazole** at the same dose levels.

L3 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2001 ACS
1975:603401 Document No. 83:203401 Covalent binding of bilirubin to agarose and use of the product for affinity chromatography of serum albumin. Hierowski, Marian; Brodersen, Rolf (Inst. Med. Biochem., Univ. Aarhus, Aarhus, Den.). Lipmann Symp.: Energy, Regul. Biosynth. Mol. Biol., 281-97. Editor(s): Richter, Dietmar. de Gruyter: Berlin, Ger. (English) 1974. CODEN: 31NGAV.
AB A method was described for the covalent coupling of bilirubin to agarose through the aminohexylamino group by using a carbodiimide reagent. The product contained 1.1 .mu.moles bilirubin/ml packed gel (250 mg dry wt.) and could reversibly bind 0.08 .mu.moles rat serum albumin. Elution was

effected by salicylate and **sulfisoxazole**, substances competing for the high-affinity bilirubin site on albumin, and by 8M urea. Albumin could be sepd. from human serum by affinity chromatog. on this material. Lengthening of the aminoalkylamino arm increased the capacity for albumin, but also increased binding of other serum proteins.

L3 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2001 ACS
1971:63438 Document No. 74:63438 Evidence of safety of long-term, high, oral doses of DDT for man. Hayes, Wayland J., Jr.; Dale, William E.; Pirkle, Carl I. (Natl. Commun. Dis. Cent., Public Health Serv., Atlanta, Ga., USA). Arch. Environ. Health, 22(1), 119-35 (English) 1971. CODEN: AEHLAU.

AB In a 4-year study of effects of oral administration of DDT, 24 persons completed the study, of whom 4 were controls, 6 received 3.5 mg/day and 6 received 35 mg/day of 85% p,p'-DDT, and 8 received 35 mg/day of recrystd. p,p'-DDT for 21.5 months. Nine of the subjects reported improved appetite without increase of wt. after receiving DDT. Av. wt. in all groups decreased during the study. Arteriosclerotic heart disease and hepatitis occurred in 2 subjects receiving DDT. Other illnesses and results of neurolog. tests showed no relation to DDT dose. There was no apparent effect of DDT on results of blood tests, cardiovascular status, liver function, carbonic anhydrase activity, or gait. Storage of DDT in abdominal fat in controls was 16-30 ppm; in subjects receiving 3.5 mg/day, 35 mg/day DDT, and 35 mg/day recrystallized DDT it was 39-76, 105-619, and 129-659 ppm, resp. A steady state was probably attained by 18.8 months of dosing. After 25.5 months after dosing was discontinued, storage of DDT in the groups who received 35 mg/day was reduced to 32 and 35%, resp., of the max. level stored. DDE concns. continued to increase for a time after cessation of dosing and decreases were slight a year after cessation of dosing. Excretion of DDA (bis(p-chlorophenyl)acetic acid) decreased gradually after cessation of dosing but was still above control levels 25.5 months after the last dose in the 35 mg/day groups. Interference of the drug **sulfisoxazole** was noted in the DDA detn. Less than 20% of the doses were recovered in the feces which may show that a major part of the DDT in feces is in the form of polar **conjugates** of metabolites. A high degree of safety of the 0.063 mg/day av. intake of total DDT-related substances by man is indicated.

L3 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2001 ACS
1972:81655 Document No. 76:81655 Mode of action of antileprous drugs. III. Demasking of several N-**conjugates** of sulfonamide-type drugs by various strains of microorganisms. Tsutsumi, Sadae; Sakamoto, Yoshiki; Gidoh, Seiichi; Nakamura, Kazuaki (Natl. Inst. Leprosy Res., Tokyo, Japan). Repura, 39(3-4), 239-45 (Japanese) 1970. CODEN: REPUAC.

AB N-substituted derivs. of dapsone (I) [80-08-0], sulfamethoxypyridazine [80-35-3], and of **sulfisoxazole** [127-69-5] were deacylated by rapidly growing mycobacterial strains such as Mycobacterium fortuitum and M. tuberculosis var avium AVT. The acetyl group at N1 was more susceptible than N4 to the metabolic cleavage by NQ bacilli. When monoacetyl I was incubated with crude cell free extract of M. phlei at pH 6-8, at 37.deg. for 24 hr, a gradual increase in the amt. of I was obsd. with time.

L3 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2001 ACS
1965:412660 Document No. 63:12660 Original Reference No. 63:2261h,2262a-d Influence of enterohepatic circulation on toxicity of drugs. Williams, R.

T.; Millburn, P.; Smith, R. L. (St. Mary's Hosp. Med. School, London). Ann. N.Y. Acad. Sci., 123(1), 110-22, discussion 122-4 (English) 1965.

AB In a study of the enterohepatic circulation of foreign compds. the fate of the compds. in the hepatic cell and the mode of transition of the compds. from the cell into the bile capillaries were considered. Preliminary findings were discussed and it was emphasized that they refer only to the rat which differs from many other species in having no gall bladder. No quaternary bases were studied. The biliary excretion of 14C-labeled PhNH2, BzOH, and PhNHCSNH2 in the rat did not occur to any appreciable extent either as the compd. or metabolite. Results on the excretion of 4-O2NC6H4CO2H, 2-HOC6H4CO2H, 3,4-(HO)2C6H3CO2H, p-H2NC6H4CO2H, p-H2NC6H4CONHCH2CO2H, 3,4-I(H2N)C6H3CO2H, 3,4-I(H2N)C6H3CONHCH2CO2H, 3,5,4-I2(H2N)C6H2CO2H, 2-H2NC6H4CO2H, 3,5,2-I2(H2N)C6H2CO2H, (p-HOC6H4)2, p-HOC6H4C6H4C6H9O7-p (C6H9O7 is glucuronido), p-HOC6H4Ph, p-C6H9O7C6H4Ph, p-H2NC6H4SO2NH2, p-H2NC6H4SO2NHAc, p-H2NC6H4SO2NHC(:NH)NH2, sulfadiazine, **sulfisoxazole**, sulfasomizole, Midicel, Madribon, and Madribon N1-glucuronide. It was suggested that if a compd. is excreted in the bile in amts. greater than 5% of the dose (50-100 mg./kg.), then the main bulk is excreted as polar **conjugates** of the original compd. or its metabolites; that excretion in the bile is related to mol. size since mols. of mol. wt. less than around 150 are not excreted even though metabolized and conjugated; that compds. contg. 2 or more aromatic rings (or their equiv. in mol. wt., such as iodo groups) tend to be excreted if they can be metabolized and conjugated; and that the occurrence of certain groups in the mol. may be implicated in biliary excretion. Since the excretion of a compd. into the intestine via the bile is largely in the form of **conjugates** such as glucuronides, glycine **conjugates**, ethereal sulfates, etc., the fate of the **conjugates** in the intestine was considered. The possible toxicological consequences of biliary excretion were discussed.

L3 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2001 ACS

1964:70674 Document No. 60:70674 Original Reference No. 60:12480g-h,12481a-b

Biliary excretion of foreign compounds in the rat. Millburn, P.; Smith, R. L.; Williams, R. T. (St. Mary's Hosp. Med. School, London). Biochem. J., 90(1), 5P (Unavailable) 1964.

AB Following intraperitoneal injection, aniline-14C, benzoic-14C acid, hippuric-14C acid, and p-nitrobenzoic acid were not secreted in the bile either as such or as metabolites in rats. Salicylic acid appeared in the bile in 1.5% amts. unchanged; protocatechuic acid was excreted, mainly as the ester glucuronide of vanillic acid (14% of dose). Coumarin was excreted (45-55%) in the bile as open-ring metabolites. Indole-14C appeared in the bile (6-7%) as indoxyl sulfate and anthranilic acid derivs. Excretion of short or medium-acting sulfonamides (sulfanilamide, sulfacetamide, sulfadiazine, **sulfisoxazole**, and sulfasomizole) was 0-4%. The long-acting sulfonamides, madribon and midicel were excreted 14 and 8%, resp., the former appearing mainly as a glucuronide. Biliary excretion (% of dose) was for p-aminobenzoic acid 3, anthranilic acid 5, 4-amino-3-iodobenzoic acid 11, 4-amino-3-iodohippuric acid 25, and 3,5-diiodoanthranilic acid 35%. All except 4-amino-3-iodohippuric acid were excreted as **conjugates**. 4-Hydroxy- and 4,4'-dihydroxybiphenyl were excreted in the bile in large amts. as glucuronides. 4,4'-Dihydroxybiphenyl monoglucuronide was excreted largely unchanged (94%). It is concluded that foreign compds. are excreted in the bile mainly as polar **conjugates**. Biliary excretion increases with mol. size. Conjugation increases mol. size and polarity of mol.

=> s FKBP

L4 2908 FKBP

=> s l4 and FK506

L5 1968 L4 AND FK506

=> s l5 and conjugate

L6 13 L5 AND CONJUGATE

=> dup remove l6

PROCESSING COMPLETED FOR L6
L7 13 DUP REMOVE L6 (0 DUPLICATES REMOVED)

=> d l7 1-13 cbib abs

L7 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2001 ACS
2001:545747 Document No. 135:133932 An in vivo screen using chemical inducers of dimerization. Cornish, Virginia W. (The Trustees of Columbia University in the City of New York, USA). PCT Int. Appl. WO 2001053355 A1
20010726, 123 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US2285 20010124. PRIORITY: US 2000-490320 20000124.
AB The subject of the invention provides a compd. having the formula: H1-X-B-Y-H2, wherein each of H1 and H2 may be the same or different and capable of binding to a receptor which is the same or different; wherein each of X and Y may be present or absent and if present, each may be the same or different spacer moiety; and wherein B is an enzyme cleavable moiety. Said compds. can be called chem. inducers of dimerization. This invention also provides a method of screening proteins for the ability to catalyze bond cleavage.

L7 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2001 ACS
2001:380753 Document No. 134:361402 Bifunctional inhibitor molecules, their use in the disruption of protein-protein interactions and therapeutic applications. Crabtree, Gerald R.; Stankunas, Kryn; Briesewitz, Roger; Wandless, Thomas (The Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 2001036612 A1 20010525, 30 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31695 20001117. PRIORITY: US 1999-PV166675 19991119.
AB Bifunctional inhibitor mols. and methods for their use in the inhibition of protein-protein interactions are provided. The subject bifunctional inhibitor mols. are **conjugates** of a target protein ligand and a blocking protein ligand, where these two moieties are optionally joined by

a linking group. In the subject methods, an effective amt. of the bifunctional inhibitor mol. is administered to a host in which the inhibition of a protein-protein interaction is desired. The bifunctional inhibitor mol. simultaneously binds to its corresponding target and blocking proteins to produce a tripartite complex that inhibits the target protein-protein interaction. The subject methods and compns. find use in a variety of applications, including therapeutic applications.

L7 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2001 ACS

2001:380414 Document No. 134:371812 Targeted bifunctional molecules and therapies based thereon. Briesewitz, Roger; Crabtree, Gerald R.; Wandless, Thomas (Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 2001035978 A1 20010525, 31 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31702 20001117. PRIORITY: US 1999-PV166580 19991119.

AB Targeted bifunctional mols. and methods for their use are provided. The subject targeted bifunctional mols. are **conjugates** of a drug moiety and a targeting moiety, where these two moieties are optionally joined by a linking group. The bifunctional mols. are further characterized in that they exhibit a modulated biodistribution upon administration to a host as compared to a free drug control. The subject targeted bifunctional mols. find use in a variety of therapeutic applications. For example, a bifunctional mol. consisting of a drug moiety covalently joined to sulfisoxazole which is extensively bound by albumin, via an inert linking group is formed. When this bifunctional mol. enters the human circulation, it is bound by albumin which keeps the drug of interest in the extracellular environment.

L7 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2001 ACS

2001:91445 Document No. 134:158472 Synthetic transcriptional modulator ligands and their use in gene regulation with chimeric proteins containing DNA-binding domains and ligand-binding domains. Verdine, Gregory L.; Nyanguile, Origene (President and Fellows of Harvard College, USA). U.S. US 6183965 B1 20010206, 38 pp., Cont.-in-part of U.S. Ser. No. 987,912. (English). CODEN: USXXAM. APPLICATION: US 1998-208057 19981209. PRIORITY: US 1997-987912 19971209.

AB Novel synthetic transcriptional modulators having at least one selected ligand linked to at least one transcriptional modulating portion are described. The transcriptional modulators of the present invention can include a ligand linked to a chem. moiety. These transcriptional modulators can be used to selectively control gene expression and to identify components of the transcriptional machinery. Thus, the covalent **conjugate** (designated L-1) of **FK506** and a 29-amino acid peptide of herpes simplex virus VP16 activator domain stimulates transcription in the presence of the chimeric GAL4-**FKBP** protein, but was unable to stimulate in the absence of GAL4-**FKBP** and the activation potential was significantly reduced in the presence of added rapamycin or GST-**FKBP**. Since acyclic peptides having the natural L stereochem. configuration are highly susceptible to proteolysis, the analogous **conjugate** (D-1) bearing nonnatural D stereochem. is prepd. D-1 reproducibly stimulated transcription to a significant extent, though to a slightly lesser extent than L-1. The synthesis of a combinatorial compd. library is also provided, and various library

components are active transcriptional modulators when coupled to the HATU analog of **FK506**.

L7 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2001 ACS

2000:409167 Document No. 133:359612 The FK520 gene cluster of Streptomyces hygroscopicus var. ascomyceticus (ATCC 14891) contains genes for biosynthesis of unusual polyketide extender units. Wu, K.; Chung, L.; Revill, W. P.; Katz, L.; Reeves, C. D. (Kosan Biosciences Inc., Hayward, CA, 94545, USA). Gene, 251(1), 81-90 (English) 2000. CODEN: GENED6. ISSN: 0378-1119. Publisher: Elsevier Science B.V..

AB FK520 (ascomycin) is a macrolide produced by Streptomyces hygroscopicus var. ascomyceticus (ATCC 14891) that has immunosuppressive, neurotrophic and antifungal activities. To further elucidate the biosynthesis of this and related macrolides, we cloned and sequenced an 80 kb region encompassing the FK520 gene cluster. Genes encoding the three polyketide synthase (PKS) subunits (fkbB, fkbC and fkbA), the peptide synthetase (**fkbP**), the 31-O-methyltransferase (fkbM), the C-9 hydroxylase (fkbD) and the 9-hydroxyl oxidase (fkbO) had the same organization as the genes reported in the **FK506** gene cluster of Streptomyces sp. MA6548 (Motamedi, H. and Shafiee, A., 1998). Disruption of a PKS gene in the cluster using the .phi.C31 phage vector, KC515, led to antibiotic non-producing strains, proving the identity of the cluster. Previous labeling data have indicated that FK520 biosynthesis uses novel polyketide extender units (Byrne, K.M., et al., 1993). Genes in the flanking regions of the FK520 cluster were identified that appear to be involved in synthesis of these extender units. All but two of these genes were homologous to genes with known function. In addn. to a crotonyl-CoA reductase gene (fkbS), at least two other genes are proposed to be involved in biosynthesis of the atypical PKS extender unit ethylmalonyl-CoA, which accounts for the Et side chain on C-21 of FK520. A set of five contiguous genes (fkbGHIJK) is proposed to be involved in biosynthesis of an unusual PKS extender unit bearing an oxygen on the .alpha.-carbon, and leading to the 13- and 15-methoxy side chains. These putative precursor synthesis genes in the flanking regions of the FK520 cluster are not found in the flanking regions of the rapamycin cluster (Molnar, I., et al., 1996), consistent with labeling data showing that rapamycin biosynthesis uses only malonyl and methylmalonyl extender units.

L7 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2001 ACS

1999:763899 Document No. 132:15629 Bifunctional molecules and therapies based thereon. Briesewitz, Roger; Crabtree, Gerald R.; Wandless, Thomas; Ray, Gregory Thomas; Vogel, Kurt William (The Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 9961055 A1 19991202, 67 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US11296 19990521. PRIORITY: US 1998-86451 19980522.

AB Non-naturally occurring bifunctional **conjugates** Z-L-X (Z = ligand that binds to a specific presenter protein; X = drug moiety; L = optional linker) are provided such that upon entering a cell, Z can bind to its receptor protein (if present) and the effectiveness of X is thereby enhanced or inhibited, depending on the nature of the receptor for Z. Thus, a bifunctional peptide (I) was prepd. which contained **FK506** coupled to phosphotyrosyl-glutamyl-glutamyl-isoleucine (pYEEI), which binds to the SH2 domains of tyrosine kinases Fyn and Lck and to the

N-terminal SH2 domain of phospholipase C.gamma. (PLC.gamma.). In the presence of **FK506**-binding protein 52 (FKBP52), I bound the Fyn SH2 domain with 3-fold increased affinity. This effect was reversed by **FK506**, and was not mimicked by FKBP12 despite the similar structure of its binding domain to that of FKBP52; the increase in affinity with FKBP52 was presumably based on favorable protein-protein interactions between the Fyn SH2 domain and FKBP52. On the other hand, formation of a FKBP12-I complex reduced the affinity of I for the PLC.gamma. SH2 domain but not for the Fyn or Lek SH2 domains, suggesting that formation of a binary complex may lead to unfavorable protein-protein interactions between the presenter protein and some targets but not other targets of the drug; therefore, formation of a complex between a bifunctional mol. and a presenter protein can be used to create specificity. The cell selectivity of a bifunctional **conjugate** may be enhanced if the formation of a binary complex reduces binding of the drug to all of its targets in a cell that contains the presenter mol.; if an organism has cells that contain the presenter protein and other cells that do not, the cells lacking the presenter protein will be more affected by the bifunctional **conjugate** than cells expressing the presenter. Similarly, conjugation of penicillamine (an alk. phosphatase inhibitor) to p-aminosalicylic acid (a ligand for albumin) via glycine modulated the inhibitory activity of penicillamine toward 4 isoforms of alk. phosphatase in the presence of 100 .mu.M serum albumin, but not toward 8 other isoforms.

L7 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2001 ACS

1999:390464 Document No. 131:39762 Method to identify transcriptional modulators. Verdine, Gregory L.; Nyanguile, Origene (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 9930164 A1 19990617, 90 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US26101 19981209. PRIORITY: US 1997-987912 19971209.

AB Novel synthetic transcriptional modulators having at least one selected ligand linked to at least one transcriptional modulating portion are described. The transcriptional modulators of the present invention can include a ligand linked to a chem. moiety. These transcriptional modulators can be used to selectively control gene expression and to identify components of the transcriptional machinery.

L7 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2001 ACS

1999:314417 Document No. 131:84996 Clonal selection and in vivo quantitation of protein interactions with protein-fragment complementation assays. Remy, Ingrid; Michnick, Stephen W. (Departement de Biochimie, Universite de Montreal, Montreal, PQ, H3C 3J7, Can.). Proc. Natl. Acad. Sci. U. S. A., 96(10), 5394-5399 (English) 1999. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB Two strategies are described for detecting constitutive or induced protein-protein interactions in intact mammalian cells; these strategies are based on oligomerization domain-assisted complementation of rationally designed fragments of the murine enzyme dihydrofolate reductase (DHFR; EC 1.5.1.3). We describe a dominant clonal-selection assay of stably transfected cells expressing partner proteins **FKBP** (**FK506** binding protein) and FRAP (**FKBP**-rapamycin binding protein) fused to DHFR fragments and show a rapamycin dose-dependent survival of clones that requires .apprxeq.25 mols. of reconstituted DHFR per cell. A fluorescence assay also is described, based on stoichiometric binding of fluorescein-methotrexate to reconstituted DHFR in vivo.

Formation of the **FKBP**-rapamycin-FRAP complex is detected in stably and transiently transfected cells. Quant. rapamycin dose-dependence of this complex is shown to be consistent with in vitro binding and distinguishable from a known constitutive interaction of **FKBP** and FRAP. We also show that this strategy can be applied to study membrane protein receptors, demonstrating dose-dependent activation of the erythropoietin receptor by ligands. The combination of these clonal-selection and fluorescence assays in intact mammalian cells makes possible selection by simple survival, flow cytometry, or both. High-throughput drug screening and quant. anal. of induction or disruption of protein-protein interactions are also made possible.

L7 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2001 ACS
1998:640407 Document No. 129:272665 High throughput assays using fusion proteins for screening binding compounds and protease inhibitors. Hermes, Jeffrey D.; Salowe, Scott P.; Sinclair, Peter J. (Merck & Co., Inc., USA).
PCT Int. Appl. WO 9841866 A1 19980924, 42 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US4610 19980310. PRIORITY: US 1997-40795 19970314.
AB This application describes a high throughput assay for screening compds. which are capable of binding to a fusion protein which consists of a target protein and an **FK506**-binding protein. This application also describes an assay for screening compds. which inhibit a protease. A **FK506**-binding protein-ZAP70 tandem SH2 domains fusion protein was recombinantly prepd., expressed in Escherichia coli, and purified by affinity chromatog. on agarose-immobilized avidin having bound biotinylated phosphopeptide derived from the .zeta.1 ITAM sequence of the human T-cell receptor. Inhibitors of the fusion protein are screened using the biotinylphosphopeptide, the fusion protein, and europium cryptate-labeled **FK506** analog in wells of a 96-well black microplate. The fluorescence ratio is measured in a Packard Discovery homogeneous time-resolved fluorescence analyzer.

L7 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2001 ACS
1998:457205 Document No. 129:78842 High throughput ligand assay using fusion proteins based on FK 506-binding protein. Salowe, Scott P. (Merck and Co., Inc., USA). U.S. US 5776696 A 19980707, 14 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-707793 19960904.
AB This invention covers a method of screening for compds. capable of binding to a fusion protein in which the screening system consists of a test compd., a tagged ligand, a fusion protein (target protein, peptide linker and FK 506-binding protein), a radiolabeled ligand, and coated scintillation proximity assay (SPA) beads, and then measuring the scintillation counts attributable to the binding of the tagged ligand to the fusion protein in the presence of the test compd. relative to a control assay in the absence of the test compd., so as to det. the effect the test compd. has on the binding of the tagged ligand. This invention provides an immediate means of making use of SPA technol. for the functional assay of ligand binding to a single or multiple signal transduction domains(s), for example a phosphopeptide binding to an SH2 domain. The present invention does not require specialized radiochem. synthesis and is readily adaptable to robotic automation for high capacity screening for agonists, antagonists and/or inhibitors.

L7 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2001 ACS
1997:740333 Document No. 128:10873 A three-hybrid reporter gene method for

screening for proteins binding defined ligands. Liu, Jun; Licitra, Edward J. (Massachusetts Institute of Technology, USA). PCT Int. Appl. WO 9741255 A1 19971106, 40 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US6912 19970425. PRIORITY: US 1996-17341 19960426.

AB A method for identifying the binding partner for a define ligand using an extension of the two-hybrid system is described. The method uses a fusion protein of the LexA protein and a ligand binding protein to bind to a LexA operator upstream of a reporter gene. This is bound to by a **conjugate** of the natural ligand for the protein and the ligand of interest. Possible binding partners for the ligand are identified by introduction of an expression library in which the proteins are synthesized as fusion products with a transcriptional activator. When the necessary combination of LexA fusion protein, ligand, and transcriptional activator fusion protein are brought together, the reporter gene is expressed. The method is particularly intended for the identification of natural binding partners for small mols. A fusion product of LexA and the rat glucocorticoid receptor is used in a reconstruction expt. with **FK506**-binding protein FKBP12 is used to demonstrate using a **conjugate** of dexamethasone and **FK506** as the hybrid ligand.

L7 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2001 ACS

1997:286410 Document No. 126:259161 A high throughput assay for modulators of protein domain interaction using FK-506-binding proteins as reporter moieties in fusion proteins. Salowe, Scott P. (Merck and Co., Inc., USA; Salowe, Scott P.). PCT Int. Appl. WO 9710502 A1 19970320, 27 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US14563 19960911. PRIORITY: US 1995-3824 19950915; GB 1996-3486 19960220.

AB A high throughput scintillation proximity assay (SPA) for screening for compds. capable of binding to a fusion protein of a target protein and an **FK506**-binding protein (**FKBP**) that avoids the need to prep. labeled ligands for the target protein is described. The assay is particularly intended for screening of ligands modulating the binding of protein kinases to SH domains, esp. SH2 domains. The **FKBP** fusion protein is labeled with a tritiated FK-506 deriv. and binding of the fusion protein to the peptide is measured by the radioactivity bound to SPA beads carrying the SH2 domain. The SH2 domain can be immobilized on SPA beads by std. methods such as a biotin/streptavidin couple or via an antibody **conjugate** or fusion protein. The prepn. of fusion proteins of the human 12 kilodalton **FKBP** and Syk kinase, ZAP-70, and p56lck is reported.

L7 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2001 ACS

1991:485367 Document No. 115:85367 Detection of noncovalent receptor-ligand complexes by mass spectrometry. Ganem, Bruce; Li, Yu Tsyr; Henion, Jack D. (Dep. Chem., Cornell Univ., Ithaca, NY, 14853, USA). J. Am. Chem. Soc., 113(16), 6294-6 (English) 1991. CODEN: JACSAT. ISSN: 0002-7863.

AB Few methods are known for detecting and identifying enzyme-substrate, receptor-ligand and antibody-antigen complexes, whose weak noncovalent interactions constitute the essential basis of mol. recognition in the biol. world. This manuscript describes the use of ion-spray mass spectrometry to detect noncovalent receptor-ligand complexes formed between the immunosuppressive agents **FK506** (MW 804 Da) and rapamycin (RM, MW 913 Da) with their naturally-occurring cytoplasmic

receptor **FKBP** (MW 11,812 Da) a member of the immunophilin family of immunosuppressive binding proteins. The immunophilin binds both **FK506** (Kd = 0.4 nM, pH 7.8) and RM (Kd = 0.2 nM) with high affinity. When **FKBP** was mixed with a slight molar excess of **FK506** at pH 7.5 (receptor-ligand 1:1.6), a new signal appeared at m/z 1803.1, corresponding to the **FKBP**-**FK506** complex in the 7+ charge state. Binding of **FKBP** with RM (1:1.6 ratio, pH 7.5) was also readily detected, giving rise to signals at m/z 1821.3 and 2124.4 for the (**FKBP**+RM+NH4+6H)7+ and (**FKBP** +RM+NH4+5H)6+ charge states, resp., of the receptor-ligand complex. Control expts. established that the new signals were not due to nonspecific protein-ligand binding. The expts. described here also suggest that other receptor-ligand or enzyme-substrate complexes may be detectable under conditions which are compatible with ion-spray mass spectrometry.

=> s methotrexate

L8 130000 METHOTREXATE

=> s l8 and bifunctional

L9 178 L8 AND BIFUNCTIONAL

=> s l9 and conjugate

L10 3 L9 AND CONJUGATE

=> dup remove l10

PROCESSING COMPLETED FOR L10
L11 3 DUP REMOVE L10 (0 DUPLICATES REMOVED)

=> d l11 1-3 cbib abs

L11 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
1995:435900 Document No. 122:197024 Polymeric carriers for noncovalent drug conjugation. Gustavson, Linda M.; Anderson, David C.; Morgan, Alton C., Jr. (Neorx Corp., USA). PCT Int. Appl. WO 9503064 A1 19950202, 62 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US7734 19940712. PRIORITY: US 1993-95515 19930726.

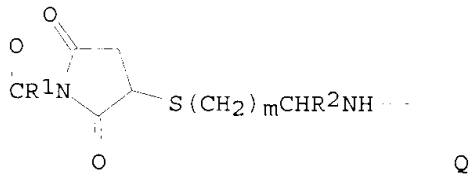
AB Polymeric carriers are polypeptides comprising .gtoreq.1 drug-binding domain that noncovalently binds a drug. A polymeric carrier may be attached to an antibody specific for desired target cells to form immunoconjugates that deliver a drug to the target cells in vivo. A polymeric carrier may be attached to a proteinaceous or nonproteinaceous ligand or anti-ligand to form a **conjugate** useful in pretargeting protocols to deliver a drug to target cells in vivo. The carriers are derived from drug-binding proteins and produced through peptide synthesis or recombinant DNA technol. Thus, chicken riboflavin-binding protein, which noncovalently binds adriamycin, was reduced with DTT in the presence of guanidine-HCl and digested with CNBr, and fragments which tightly bound adriamycin were isolated by gel filtration of the adriamycin complex and crosslinked e.g. via lysine residues with bis(sulfosuccinimidyl) suberate. The resulting polymer was attached to a targeting protein, e.g. an antibody, with a **bifunctional** crosslinker such as succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate.

L11 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2001 ACS
1990:156562 Document No. 112:156562 Polysaccharide-modified immunoglobulins having reduced immunogenic potential and unaltered or improved pharmacokinetics. Fagnani, Roberto Cesare (Hybritech, Inc., USA). Eur. Pat. Appl. EP 315456 A2 19890510, 50 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1988-310372 19881103. PRIORITY: US 1987-118150 19871105.

AB An Ig, or fragment thereof, is conjugated with a modified low-mol.-wt. polysaccharide, preferably an oxidized dextran. The conjugated Igs, usable in immunotherapeutic and immunodiagnostic compn., show unaltered immunoreactivity, unaltered or improved pharmacokinetics, but reduced immunogenicity, compared to the unmodified Ig. The Ig may be bound to a drug (Adriamycin, **methotrexate**, cisplatin, etc.) or to a chelating agent. Dextran was oxidized with NaIO4 in Na borate buffer (pH 3.1). The monoclonal antibody T101 was conjugated with the oxidized dextran in Na phosphate buffer (pH 6.5-7.5) in the presence of NaBH3CN. The remaining free aldehyde groups were reduced with NaBH4. Conjugation did not alter the immunoreactivity of T101, as shown in an assay using the human T-cell line T-8402, which possesses an antigen recognized by T101. The decreased immunogenicity of the **conjugates** was shown by injection into rabbits, followed by measuring the anti-mouse response in the serum by the conventional ELISA technique. **Bifunctional**, chimeric (including humanized), and **bifunctional**-chimeric antibodies may also be used.

L11 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS
1988:622460 Document No. 109:222460 **Conjugates** containing tumor-specific agents, cytotoxic agents and biodegradable polymeric carriers for selective delivery of cytotoxic drugs to tumor cells and methods of destroying tumor cells using the **conjugates**. Myers, Andrew; Bichon, Daniel (Battelle Memorial Institute, Switz.). PCT Int. Appl. WO 8800837 A2 19880211, 44 pp. DESIGNATED STATES: W: AU, BR, DK, FI, JP, KR, NO. (English). CODEN: PIXXD2. APPLICATION: WO 1987-EP435 19870805. PRIORITY: EP 1986-810347 19860807.

GI



AB A novel drug **conjugate** for destroying tumor cells comprises (a) a 1st moiety (homing agent), other than an Ig or Ig fragment, which preferentially binds to a tumor cell and (b) a 2nd moiety linked to the 1st comprising a biodegradable polymeric carrier C(O)CH(NH)(CH2)pC(O)AxT (I; p, x = integers; Ax = **bifunctional** linker; T = OH, cytotoxic substance). The **conjugate** is internalized by tumor cells. The degrdn. of the carrier by intracellular enzymes releases the cytotoxic agents, resulting in destruction of the cell. Alternatively, the linking group is Q (R1 = C1-4 alkylene, 1,3-phenylene, cyclohexylene-4-methylene, C1-4 alkylene-1,4-phenylene; R2 = H, CO2H; m = 1,2). A **conjugate** of epidermal growth factor (EGF) and daunomycin-grafted polyglutamic acid: EGF-Q-I [R1 = (CH2)3; m = 1; R2 = H; p = 2; x = O; T = OH, daunomycin in a ratio of 6:1] was prepd. and tested in nude mice injected with 5 .times. 106 human squamous carcinoma A431 cells. The tumor growth coeff. was

16.4, 2.2, and 35.6 for mice treated i.v. with 0.1 mg free daunomycin/kg, 0.1 mg daunomycin in **conjugate**/kg, and control (placebo), resp.

=> s quinacrine

L12 11596 QUINACRINE

=> s l12 and conjugate

L13 43 L12 AND CONJUGATE

=> s l13 and bifunctional

L14 1 L13 AND BIFUNCTIONAL

=> d l14 cbib abs

L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
2001:380414 Document No. 134:371812 Targeted **bifunctional** molecules and therapies based thereon. Briesewitz, Roger; Crabtree, Gerald R.; Wandless, Thomas (Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 2001035978 A1 20010525, 31 pp.
DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31702 20001117. PRIORITY: US 1999-PV166580 19991119.
AB Targeted **bifunctional** mols. and methods for their use are provided. The subject targeted **bifunctional** mols. are **conjugates** of a drug moiety and a targeting moiety, where these two moieties are optionally joined by a linking group. The **bifunctional** mols. are further characterized in that they exhibit a modulated biodistribution upon administration to a host as compared to a free drug control. The subject targeted **bifunctional** mols. find use in a variety of therapeutic applications. For example, a **bifunctional** mol. consisting of a drug moiety covalently joined to sulfisoxazole which is extensively bound by albumin, via an inert linking group is formed. When this **bifunctional** mol. enters the human circulation, it is bound by albumin which keeps the drug of interest in the extracellular environment.

=> dup remove l14

PROCESSING COMPLETED FOR L14
L15 1 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> dup move l13

ENTER REMOVE, IDENTIFY, ONLY, OR (?):l13

'L63' IS NOT VALID HERE
Enter "REMOVE" to identify and remove duplicate answers.
Enter "IDENTIFY" to identify duplicate answers in the answer set.
Enter "ONLY" to identify and create an answer set containing only

duplicate records.
ENTER REMOVE, IDENTIFY, ONLY, OR (?):only

'MOVE' IS VALID ONLY WITH THE REMOVE OPTION
File names can only be entered when using the REMOVE option of the
DUPLICATE command.

=> d his

(FILE 'HOME' ENTERED AT 13:17:55 ON 19 SEP 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 13:18:11 ON
19 SEP 2001
L1 3046 S SULFISOXAZOLE
L2 37 S L1 AND CONJUGATE
L3 19 DUP REMOVE L2 (18 DUPLICATES REMOVED)
L4 2908 S FKBP
L5 1968 S L4 AND FK506
L6 13 S L5 AND CONJUGATE
L7 13 DUP REMOVE L6 (0 DUPLICATES REMOVED)
L8 130000 S METHOTREXATE
L9 178 S L8 AND BIFUNCTIONAL
L10 3 S L9 AND CONJUGATE
L11 3 DUP REMOVE L10 (0 DUPLICATES REMOVED)
L12 11596 S QUINACRINE
L13 43 S L12 AND CONJUGATE
L14 1 S L13 AND BIFUNCTIONAL
L15 1 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> dup remove l13

PROCESSING COMPLETED FOR L13
L16 20 DUP REMOVE L13 (23 DUPLICATES REMOVED)

=> d l16 1-20 cbib abs

L16 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2001 ACS
2001:380414 Document No. 134:371812 Targeted bifunctional molecules and
therapies based thereon. Briesewitz, Roger; Crabtree, Gerald R.;
Wandless, Thomas (Board of Trustees of the Leland Stanford Junior
University, USA). PCT Int. Appl. WO 2001035978 A1 20010525, 31 pp.
DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
BZ,
CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY,
DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE,
SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31702
20001117. PRIORITY: US 1999-PV166580 19991119.
AB Targeted bifunctional mols. and methods for their use are provided. The
subject targeted bifunctional mols. are **conjugates** of a drug
moiety and a targeting moiety, where these two moieties are optionally
joined by a linking group. The bifunctional mols. are further
characterized in that they exhibit a modulated biodistribution upon
administration to a host as compared to a free drug control. The subject
targeted bifunctional mols. find use in a variety of therapeutic
applications. For example, a bifunctional mol. consisting of a drug
moiety covalently joined to sulfisoxazole which is extensively bound by
albumin, via an inert linking group is formed. When this bifunctional
mol. enters the human circulation, it is bound by albumin which keeps the

drug of interest in the extracellular environment.

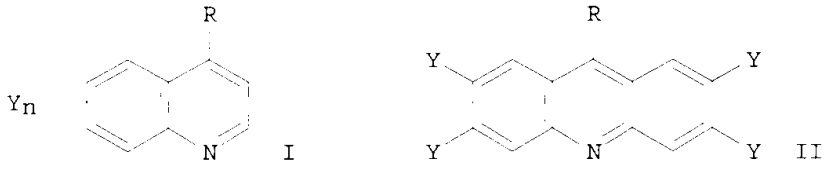
L16 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2001 ACS
2000:368704 Document No. 133:14300 In situ method of analyzing cells by staining with multiple stains and using a spectral data collection device.
Garini, Yuval; Mcnamara, George; Soenksen, Dirk G.; Cabib, Dario; Buckwald, Robert A. (Applied Spectral Imaging Ltd., Israel). PCT Int. Appl. WO 2000031534 A1 20000602, 129 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English) CODEN: PIXXD2. APPLICATION: WO 1999-US27000 19991116. PRIORITY: US 1998-196690 19981120.
AB A method of in situ anal. of a biol. sample comprises the steps of (a) staining the biol. sample with N stains of which a first stain is selected from the group consisting of a first immunohistochem. stain, a first histol. stain and a first DNA ploidy stain, and a second stain is selected from the group consisting of a second immunohistochem. stain, a second histol. stain and a second DNA ploidy stain, with provisions that N is an integer greater than three and further that (i) if the first stain is the first immunohistochem. stain then the second stain is either the second histol. stain or the second DNA ploidy stain; (ii) if the first stain is the first histol. stain then the second stain is either the second immunohistochem. stain or the second DNA ploidy stain; whereas (iii) if the first stain is the first DNA ploidy stain then the second stain is either the second immunohistochem. stain or the second histol. stain; and (b) using a spectral data collection device for collecting spectral data from the biol. sample, the spectral data collection device and the N stains are selected so that a spectral component assocd. with each of the N stains is collectible. Figure (1) shows a block diagram illustrating the main components of an imaging spectrometer. Breast cancer tissue samples were stained with two histol. stains (hematoxylin and eosin), and four immunohistochem. stains (DAB, AEC, Fast Red, and BCIP/NBT) and measured using the Spectracube system.

L16 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2001 ACS
2000:459311 Document No. 133:202647 Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. Wargovich, Michael J.; Jimenez, Arnaldo; McKee, Kathy; Steele, Vernon E.; Velasco, Marco; Woods, Johnnie; Price, Roger; Gray, Kenneth; Kelloff, Gary J. (Division of Basic Research, South Carolina Cancer Center, Columbia, SC, 29203, USA). Carcinogenesis, 21(6), 1149-1155 (English) 2000. CODEN: CRNGDP. ISSN: 0143-3334. Publisher: Oxford University Press.
AB We assessed the effects of 78 potential chemopreventive agents in the F344 rat using two assays in which the inhibition of carcinogen-induced aberrant crypt foci (ACF) in the colon was the measure of efficacy. In both assays ACF were induced by the carcinogen azoxymethane (AOM) in F344 rats by two sequential weekly injections at a dose of 15 mg/kg. Two weeks after the last AOM injection, animals were evaluated for the no. of aberrant crypts detected in methylene blue stained whole mounts of rat colon. In the initiation phase protocol agents were given during the period of AOM administration, whereas in the post-initiation assay the chemopreventive agent was introduced during the last 4 wk of an 8 wk assay, a time when ACF had progressed to multiple crypt clusters. The agents were derived from a priority listing based on reports of chemopreventive activity in the literature and/or efficacy data from in

vitro models of carcinogenesis. During the initiation phase carboxyl amidoimidazole, p-chlorphenylacetate, chlorpheniramine maleate, D609, diclofenac, etoperidone, eicosatetraynoic acid, farnesol, ferulic acid, lycopene, meclizine, methionine, phenylhexylisothiocyanate, phenylbutyrate, piroxicam, 9-cis-retinoic acid, S-allylcysteine, taurine, tetracycline and verapamil were strong inhibitors of ACF. During the post-initiation phase aspirin, calcium glucarate, ketoprofen, piroxicam, 9-cis-retinoic acid, retinol and rutin inhibited the outgrowth of ACF into multiple crypt clusters. Based on these data, certain phytochems., antihistamines, non-steroidal anti-inflammatory drugs and retinoids show unique preclin. promise for chemoprevention of colon cancer, with the latter two drug classes particularly effective in the post-initiation phase of carcinogenesis.

L16 ANSWER 4 OF 20 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
1999269502 EMBASE Distance dependence of electron transfer in acridine-intercalated DNA. Fukui K.; Tanaka K.; Fujitsuka M.; Watanabe A.; Ito O.. K. Tanaka, Department of Molecular Engineering, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan. a51053@sakura.kudpc.kyoto-a.ac.jp. Journal of Photochemistry and Photobiology B: Biology 50/1 (18-27) 1999.
Refs: 68.
ISSN: 1011-1344. CODEN: JPPBEG.
Publisher Ident.: S 1011-1344(99)00063-9. Pub. Country: Switzerland.
Language: English. Summary Language: English.
AB The photoinduced electron-transfer reaction in a DNA helix has been studied using 9-amino-6-chloro-2-methoxyacridine (ACMA) selectively intercalated at an internucleotide site of a DNA. The photoexcited ACMA is used as an electron acceptor, and guanine in DNA as an electron donor. ACMA-DNA **conjugates** possessing guanine at 5' or 3' direction(s) with different distance(s) from the intercalated ACMA have been prepared for a systematic examination of the distance dependence of the electron-transfer reaction in a DNA helix. In DNA consisting of only the (dA-dT) base pair, the fluorescence of the singlet-excited ACMA decays in a mono-exponential manner with a longest lifetime of 22.8 ns. The fluorescence lifetime of the excited ACMA decreases with incorporation of guanosine depending on the distance between the ACMA and guanine. When an ACMA and a guanine are directly stacked, the decay lifetime markedly decreases, showing a forward electron-transfer rate, k(fet), of .simeq. 1010 s-1. Treating the kinetic data according to k(fet) = Aexp (-.beta.R), where R is the separation distance in .ANG., gives a .beta. value of 1.47 .ANG.-1. Moreover, as a model compound for ACMA, the redox potential of **quinacrine** dihydrate bi (tetrafluoroborate) has been measured by cyclic voltammetry in acetonitrile. Comparison of the redox potential with those of nucleobases has revealed that only guanine can quench the fluorescence of ACMA and a free-energy change .DELTA.G.degree.= -0.46 eV has been evaluated for this electron-transfer reaction.

L16 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2001 ACS
1998:794983 Document No. 130:33029 Nitrogen-containing heteroaryl potassium channel blockers for antiarrhythmic agents. Terrar, Derek; Gill, Edward; Mamas, Mamas (Isis Innovation Limited, UK). PCT Int. Appl. WO 9854148 A2 19981203, 23 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB1579 19980529. PRIORITY: GB 1997-11220 19970530.
GI



AB Compds. I or II (R = primary or secondary amine or LZ, Y = H, halo, alkyl, alkoxy, perfluoroalkyl, nitro, LZ, n = 1-4, L = linker chain of 1-20 C, N, O, or S; Z = calcium channel blocker) have potassium channel-blocking activity and are useful for the prophylaxis or therapy of arrhythmia.

L16 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2001 ACS
1998:502550 Document No. 129:186419 Marker for fluorescence detection isoelectric focusing electrophoresis. Matsumoto, Hiroyuki; Tsukata, Takako; Mizusawa, Yasuhiro; Takamoto, Naonobu; Shimura, Kiyohito; Wang, Shi; Kasai, Kenichi (Bunshi Bio Photonics Kenkyujo K. K., Japan). Jpn. Kokai Tokkyo Koho JP 10197481 A2 19980731 Heisei, 13 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1997-267974 19970912. PRIORITY: JP 1996-318762 19961114.
AB Markers for fluorescence detection isoelec. focusing electrophoresis are oligopeptides linked to chromogens via SH group. The fluorescence markers have a large pI value.

L16 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2001 ACS
1997:12605 Document No. 126:44637 Isoelectric point markers for isoelectric focusing with fluorescence detection. Shimura, Kiyohito; Kasai, Kenichi; Matsumoto, Hiroyuki; Takamoto, Hisayoshi (Laboratory of Molecular Biophotonics, Japan). Eur. Pat. Appl. EP 744614 A2 19961127, 29 pp. DESIGNATED STATES: R: CH, DE, LI, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1996-105113 19960329. PRIORITY: JP 1995-76873 19950331; JP 1995-271196 19951019.
AB Provided are isoelec. point (pI) markers for isoelec. focusing with fluorescence detection. The markers are fluorescence-labeled oligopeptides which comprise a fluorescent dye bonded chem. to the amino group of the N-terminal amino acid of oligopeptide. The marker shows its unique and narrow pI band (peak) in electrophoresis or isoelec. focusing. The markers can be designed to have appropriate pI value and cover a wide range of pI ($3 < pI < 11$). Further, the markers have good storage stability. The markers can be preferably applied to capillary isoelec. focusing with fluorescence detection due to their sharp and narrow band with strong emitted fluorescence.

L16 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2001 ACS
1993:642934 Document No. 119:242934 Photocleavage of DNA using organic oxyradicals. Herkstroeter, William George; Farid, Samir Yacoub; Gould, Ian Robert; Chen, Chin Hsin; Jayaraman, Krishna; Specht, Donald P. (Eastman Kodak Co., USA). PCT Int. Appl. WO 9314104 A1 19930722, 56 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US256 19930113. PRIORITY: US 1992-819905 19920113; US 1993-1362 19930107.
AB Compns. for photocleavage of DNA comprise an oligonucleotide conjugated to an org. oxyradical precursor. The precursor can produce an oxyradical by direct photoexcitation, or by accepting an electron from a dye followed by release of an oxyradical. Upon exposure of a soln. contg. the target DNA

and the **conjugate** (and a dye if necessary) to activating light, an oxyradical is produced and the sugar-phosphate backbone of the target is cleaved. Alternatively, the oligonucleotide can be conjugated to the dye. A **conjugate** of acridine orange and M13-complementary oligonucleotide was prepd. Exposure of a soln. of M13, dye-oligonucleotide **conjugate**, and oxyradical precursor 1,5-bis-(stilbazole-N-oxide)-pentane to light of appropriate wavelength resulted in cleavage of M13 in only one confined region of the entire DNA sequence.

L16 ANSWER 9 OF 20 MEDLINE DUPLICATE 2
93231420 Document Number: 93231420. PubMed ID: 8472871. Cytotoxic activity of lutropin-gelonin **conjugate** in mouse Leydig tumor cells: potentiation of the hormonotoxin activity by different drugs. Marcil J; Ravindranath N; Sairam M R. (Reproduction Research Laboratory, Clinical Research Institute of Montreal, Que., Canada.) MOLECULAR AND CELLULAR ENDOCRINOLOGY, (1993 Mar) 92 (1) 83-90. Journal code: E69; 7500844. ISSN: 0303-7207. Pub. country: Netherlands. Language: English.
AB A hormonotoxin preparation composed of gelonin, a basic protein of 30,000 Da isolated from the plant Gelonium multiflorum and the luteinizing hormone (LH, lutropin) isolated from the sheep pituitary has been studied for its cytotoxic action on mouse testicular Leydig tumor cells (MA-10 cells). Gelonin modified with 2-iminothiolane and conjugated with hormone modified by N-succinimidyl-3-2-pyridyl dithiopropionate was able to inhibit protein synthesis in Leydig tumor cells. An enhancement of the cytotoxicity of the hormonotoxin was obtained in the presence of drugs like **quinacrine**, chloroquine, verapamil and monensin. We report that the cytotoxicity of hormonotoxin was enhanced 10-15 times with **quinacrine** (7.6 microM), chloroquine (29 microM), verapamil (40 microM) and monensin (0.29 microM). While **quinacrine**, chloroquine and verapamil were not cytotoxic to MA-10 cells for up to 48 h, monensin alone reduced protein synthesis significantly in 48 h. All the drugs studied here inhibited steroidogenic action of the native hormone even at concentrations which were not detrimental to protein synthesis. On the basis of the above studies, we suggest that it may be feasible to develop combination strategies to destroy gonadal cells bearing gonadotropin (LH) receptors. In cells not bearing LH receptors (COS-7 cell line) there was no cytotoxicity either with hormonotoxin alone or in combination with the drugs, suggesting specificity of action.

L16 ANSWER 10 OF 20 MEDLINE DUPLICATE 3
91232207 Document Number: 91232207. PubMed ID: 2030576. Detection of Y chromosome by in situ hybridization in combination with membrane antigens by two-color immunofluorescence. van den Berg H; Vossen J M; Langlois van den Bergh R; Bayer J; van Tol M J. (Department of Pediatrics, Leiden University Hospital, The Netherlands.) LABORATORY INVESTIGATION, (1991 May) 64 (5) 623-8. Journal code: KZ4; 0376617. ISSN: 0023-6837. Pub. country: United States. Language: English.
AB Discrimination between donor and recipient peripheral blood cells through detection of the Y chromosome can be useful to document chimerism and engraftment after sex-mismatched bone marrow transplantation. Currently applied methods are hampered by the selection of cells (e.g., karyotyping of cells in metaphase) or by the fact that the detection of Y chromosome by in situ hybridization with specific probes does not allow further characterization of the cells. Although **quinacrine** staining of Y chromosomes can be performed on cells previously marked for membrane antigens, this staining is not fully discriminative between male and female cells. To circumvent this, a technique has been developed, in which mononuclear cells in suspension were stained for membrane antigens by the consecutive use of monoclonal antibodies and tetramethylrhodamine

isothiocyanate **conjugates**. After the cells were spun down on slides and fixed with methanol/acetic acid and formaldehyde, in situ hybridization with a biotinylated Y-chromosome-specific DNA probe was performed. The probe was detected with avidin-fluorescein isothiocyanate and the signal was amplified by consecutive incubation with biotinylated anti-avidin and avidin-fluorescein isothiocyanate. The membrane staining for various antigens remained undisturbed during the hybridization procedure and the Y probe discriminated almost completely between male and female cells. Therefore, this approach allowed us to determine the chimerism within different subpopulations of unseparated mononuclear cells after sex-mismatched bone marrow transplantation with a sensitivity of 98% and a specificity of 100%.

L16 ANSWER 11 OF 20 SCISEARCH COPYRIGHT 2001 ISI (R)
91:302724 The Genuine Article (R) Number: FM280. DETECTION OF Y-CHROMOSOME BY INSITU HYBRIDIZATION IN COMBINATION WITH MEMBRANE-ANTIGENS BY 2-COLOR IMMUNOFLUORESCENCE. VANDENBERG H (Reprint); VOSSEN J M; VANDENBERGH R L; BAYER J; VANTOL M J D. LEIDEN UNIV HOSP, DEPT PEDIAT, POB 9600, 2300 RC LEIDEN, NETHERLANDS (Reprint); TNO, INST RADIOBIOL, RIJSWIJK, NETHERLANDS.
LABORATORY INVESTIGATION (1991) Vol. 64, No. 5, pp. 623-628. Pub. country: NETHERLANDS. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Discrimination between donor and recipient peripheral blood cells through detection of the Y chromosome can be useful to document chimerism and engraftment after sex-mismatched bone marrow transplantation. Currently applied methods are hampered by the selection of cells (e.g., karyotyping of cells in metaphase) or by the fact that the detection of Y chromosome by in situ hybridization with specific probes does not allow further characterization of the cells. Although **quinacrine** staining of Y chromosomes can be performed on cells previously marked for membrane antigens, this staining is not fully discriminative between male and female cells. To circumvent this, a technique has been developed, in which mononuclear cells in suspension were stained for membrane antigens by the consecutive use of monoclonal antibodies and tetramethylrhodamine isothiocyanate **conjugates**. After the cells were spun down on slides and fixed with methanol/acetic acid and formaldehyde, in situ hybridization with a biotinylated Y-chromosome-specific DNA probe was performed. The probe was detected with avidin-fluorescein isothiocyanate and the signal was amplified by consecutive incubation with biotinylated anti-avidin and avidin-fluorescein isothiocyanate. The membrane staining for various antigens remained undisturbed during the hybridization procedure and the Y probe discriminated almost completely between male and female cells. Therefore, this approach allowed us to determine the chimerism within different subpopulations of unseparated mononuclear cells after sex-mismatched bone marrow transplantation with a sensitivity of 98% and a specificity of 100%.

L16 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2001 ACS
1990:30637 Document No. 112:30637 Protozoacide-carrier **conjugates** as antiprotozoal agents. Mirelman, David; Wilchek, Meir (Yeda Research and Development Ltd., Israel). Eur. Pat. Appl. EP 305968 A2 19890308, 10 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1988-114131 19880830.
PRIORITY: IL 1987-83715 19870831.

AB An pharmaceutical formulation contains micron-size particles of silica, Al
silicates, kaolin, latex, etc., which are ingestible by protozoa, and an antiprotozoal agent bound to said particles. The binding is by a chem. bond via a hydroxy, aldehyde or amino group. Suitable antiamebic agents are amodiaquine, bemarsal, chloroquine, colistin, diiodohydroxyquinoline, dioxanide furoate, emetine-2HCl, enterovioform, ethidium bromide, furazolidone, imidocarb, allicin, oxyquinoline, nifurtimox, nitrofurantoin, paramoxycin, **quinacrine**-2HCl, 4-aminoquinoline, 8-hydroxyquinoline, and niridazole.

L16 ANSWER 13 OF 20 MEDLINE DUPLICATE 4
88080499 Document Number: 88080499. PubMed ID: 3690677. Definition of a secondary target cell trigger during natural killer cell cytotoxicity: possible role of phospholipase A2. Deem R L; Britvan L J; Targan S R. (Department of Medicine, UCLA School of Medicine 90024.) CELLULAR IMMUNOLOGY, (1987 Dec) 110 (2) 253-64. Journal code: CQ9; 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.
AB Phospholipase A2 (PA-2) is known to be involved in many calcium-dependent cellular processes and inhibitors of PA-2 have been shown to inhibit natural killer cell-mediated cytotoxicity (NK CMC). Since the trigger stage is calcium dependent, it was postulated that this effector cell-associated enzyme may play a role in early calcium-dependent processes. To define how PA-2 might be involved in NK lysis, the effect of
both PA-2 inhibitors and exogenous PA-2 on the stages of NK lysis was examined. PA-2 inhibitors, **quinacrine** and p-bromophenacyl bromide, inhibited NK CMC at the effector cell level, but affected neither
initial target-effector cell binding nor dissociated **conjugates** during the length of the NK assay, suggesting that they block post-binding
lytic events. A calcium pulse assay showed that PA-2 inhibitors inhibit only moderately when added after calcium and only within the first 15 min,
demonstrating that these inhibitors blocked very early post-binding lytic events. Because this very early post-binding inhibitory effect was consistent with effects upon the NK trigger mechanism, the effect of exogenous PA-2 on NK lysis was tested. Pretreatment of K562 target cells but not pretreatment of peripheral blood lymphocytes (PBL) with 20 units/ml PA-2 enhanced lysis by two to eight-fold (based upon lytic units), showing its enhancing effect to be at the target cell level. Single cell assays using effector cells purified by indirect panning with monoclonal antibody NKH-1 showed that only the number of killer cells was increased. Calcium pulse assays showed that enhancement of lysis was maximum 15 min after addition of calcium and decreased rapidly thereafter,
demonstrating its effect at an early post binding stage. Additionally, PA-2 was shown to overcome inhibition by the monoclonal antibody 13.3, which has been shown to affect the trigger stage of NK lysis (post-binding
but prior to calcium dependent events). Thus, it appears that an NK cell-associated PA-2 could function by modulating the target cell surface,
revealing a structure which acts as a "secondary" trigger, subsequent to the 13.3 "trigger", requisite for activation of the NK lytic process.

L16 ANSWER 14 OF 20 MEDLINE DUPLICATE 5
87244138 Document Number: 87244138. PubMed ID: 3594487. Lysosome rich cells contain the lytic activity of lymphokine-activated killer cell populations. Agah R; Shau H; Mazumder A. CANCER IMMUNOLOGY, IMMUNOTHERAPY,
(1987) 24 (3) 247-52. Journal code: CN3; 8605732. ISSN: 0340-7004. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB Little is known regarding the effectors of lymphokine-activated killer activity. Lysosomotropic agents such as **quinacrine** can be used to positively sort for lysosome rich cells in natural killer (NK) cell populations. We therefore decided to use this agent to sort lymphokine-activated killer (LAK) cells to characterize their lysosomal content. We found that the positively sorted population contained all the LAK activity, i.e., lysis of NK-resistant tumor cells (B16 melanoma cell line), with the negatively sorted cells having no killing activity. Therefore separation of interleukin-2-incubated cells for LAK activity could be accomplished using sorting after **quinacrine** staining. The treatment of positively sorted LAK cell populations with L-leucine methyl ester, a lysosomotropic dye which inhibits killing by lysosome rich cells, caused abrogation of killing of the B16 tumor by the treated populations. Single cell **conjugate** assays were also done on these sorted cells, with positively sorted cells forming the highest and negatively sorted cells the lowest percent of **conjugates**. Our data therefore indicates the important role of lysosome rich cells in the LAK cell population in the murine system.

L16 ANSWER 15 OF 20 MEDLINE DUPLICATE 6

85276889 Document Number: 85276889. PubMed ID: 4025667. Immunoregulatory activities of human trophoblasts mediated by polyamine complexes. Remacle-Bonnet M; Culouscou J M; Pommier G; Rance R; Depieds R. AMERICAN JOURNAL OF REPRODUCTIVE IMMUNOLOGY AND MICROBIOLOGY, (1985 Jun) 8 (2) 55-61. Journal code: 3XY; 8501543. ISSN: 8755-8920. Pub. country: United States. Language: English.

AB In a previous publication we described the presence in human placenta (HP) of immunosuppressive factors inhibiting the lymphoproliferative responses to mitogen. The results of further study reported herein indicate that the substance involved is of a syncytiotrophoblastic origin, that it is thermostable to 100 degrees C for 1 hr, and of low molecular weight, i.e. 3,500. It was defined as a polyamine **conjugate** with nucleic acids. Trophoblast cell extracts lost their immunosuppressive ability after heating in cultures of human lymphocytes supplemented with 5% autologous serum. These effects were, however, preserved both in cultures assayed in 5% fetal calf serum and in those to which purified polyamine oxidase (PAO) was added to autologous serum. Trophoblast cell extract was found to contain polyamine oxidases. Placental PAO can be inhibited by **quinacrine** a typical inhibitor of flavoprotein enzymes but not by isoniazid, an inhibitor of pyridoxal enzymes; this would suggest that the enzymes in human placenta are of a tissular rather than seric origin. The implication of these observations is that immunosuppression is mediated by oxidative products issued from an interaction between polyamine and polyamine oxidase in the syncytiotrophoblast cytosol. This interaction may constitute the basis for a local immunological barrier and may be involved in the protection of the fetus against maternal immune rejection.

L16 ANSWER 16 OF 20 MEDLINE DUPLICATE 7

84117346 Document Number: 84117346. PubMed ID: 6363922. Purification and characterization of an aminopeptidase from Plasmodium falciparum. Vander Jagt D L; Baack B R; Hunsaker L A. MOLECULAR AND BIOCHEMICAL PARASITOLOGY, (1984 Jan) 10 (1) 45-54. Journal code: NOR; 8006324. ISSN: 0166-6851. Pub. country: Netherlands. Language: English.

AB A soluble aminopeptidase from Plasmodium falciparum was purified by high performance liquid chromatography. The enzyme has a molecular weight of 100 000 and pI 6.8. Activity can be monitored conveniently with L-alanine-p-nitroanilide or L-leucine-p-nitroanilide at 405 nm or with

L-leucine-7-amido-4-methylcoumarin in a fluorescence assay. The enzyme is inhibited by bestatin and phosphoramidone but not by leupeptin, chymostatin, antipain or pepstatin. pH-rate studies indicated the presence of a group on the free enzyme, pKa = 6.6, which must be in the **conjugate** base form for activity. The aminopeptidase has an essential sulfhydryl group at the active site which is rapidly modified by Hg2+ or Zn2+, is slowly modified by p-hydroxymercuribenzoate, but is not accessible to iodoacetamide or N-ethylmaleimide. The aminopeptidase is inhibited noncompetitively by chloroquine, mefloquine and **quinacrine** (Ki = 410, 280 and 20 microM, respectively) but is not inhibited by quinine or primaquine. Hemin does not inhibit. Complexation of hemin with **quinacrine** prevents inhibition by **quinacrine**.

L16 ANSWER 17 OF 20 MEDLINE DUPLICATE 8
82025357 Document Number: 82025357. PubMed ID: 7284992. Immunochemistry of **conjugates** prepared from serum albumins and acridine nitrogen mustards (ICR mutagens). Creech H J; O'Connell A P. CANCER RESEARCH, (1981 Oct) 41 (10) 3844-51. Journal code: CNF; 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Antibodies elicited in rabbits by immunization with **conjugates** prepared from serum albumins and nitrogen mustard derivatives of **quinacrine** (atebrin) were found to have strong binding sites complementary to the **quinacrine** hapten. The characteristic absorption spectrum of **quinacrine** made possible accurate determinations of the antigen-antibody composition of the serological precipitates. Conclusive evidence that such antibodies, in addition to reacting with the **quinacrine** component of heterologous protein test **conjugates**, bind **quinacrine** itself, as well as closely related acridine haptens, was provided by quantitative inhibition studies. Atebrin and the hydroxy precursors of several heterocyclic nitrogen mustards caused more than a 50% inhibition of the antigen-antibody reactions. The antibodies elicited by the **quinacrine**-protein **conjugates** in ascites tumor-bearing mice substantially neutralized the antitumor effectiveness of the low dosages (0.5 to 2.0 mumol/kg) of the acridine nitrogen mustards that were required for a demonstration of chemotherapeutic activity. In contrast, nitrogen mustard, which has no **quinacrine** moiety, was not affected. Immunization with unaltered serum albumin had no influence on the activity of the acridine nitrogen mustards. Quantitative in vitro inhibition studies allowed satisfactory predictions in vivo immunological reactivity.

L16 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2001 ACS
1981:585347 Document No. 95:185347 Delayed-type hypersensitivity as revealed on the footpads of mice to azobenzenearsonate-acetyl bovine serum albumin.
Ohuchi, Kazuo; Yoshino, Shin; Kurihara, Atsushi; Yoshimura, Hiromitsu; Ishiguro, Masamichi; Kiso, Satoko; Tsurufuji, Susumu (Fac. Pharm. Sci., Tohoku Univ., Sendai, 980, Japan). Int. Arch. Allergy Appl. Immunol., 66(4), 395-407 (English) 1981. CODEN: IAAAAM. ISSN: 0020-5915.

AB A strong delayed-type footpad reaction was established in mice using azobenzenearsonate-acetyl bovine serum albumin (ABA-AcBSA) as an antigen. Male ddY/S mice were sensitized by s.c. injection of 100 .mu.L of Freund's complete adjuvant-saline (1:1) emulsion contg. 100 .mu.g of the antigen and challenged by s.c. injection of 2.5 .mu.L of Freund's incomplete adjuvant-saline (1:1) emulsion with 2.5 .mu.g antigen in the footpad on the 10th day after the sensitization. The anal. of the system, which fulfilled criteria for delayed-type hypersensitivity with regard to

kinetics, passive transfer and histol. of the footpad reaction, and the effect of dexamethasone, indomethacin, and **quinacrine** on the footpad reaction, is described.

L16 ANSWER 19 OF 20 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 9
77014962 EMBASE Document No.: 1977014962. Fluorescence of **quinacrine** mustard conjugated to proteins. Chen R.F.. Lab. Techn. Developm., Nat. Heart Lung Inst., Bethesda, Md. 20014, United States. Archives of Biochemistry and Biophysics 172/1 (39-50) 1976.
CODEN: ABBIA4. Language: English.

AB Proteins are readily labeled by **quinacrine** mustard to yield **conjugates** whose spectral properties are well suited for fluorescence studies. Data on these **conjugates** and on the parent compound, **quinacrine**, are presented including lifetimes, quantum yields, and corrected excitation and emission spectra. Polarization studies using the Perrin Weber equation show that rotational relaxation times can be obtained with **quinacrine** mustard **conjugates** . Such **conjugates** had lifetimes ranging from 4 to 13 ns and quantum yields from about 0.1 to 0.3. **Quinacrine** mustard is a useful reporter group, as shown by the changes in fluorescence parameters of **conjugates** undergoing conformational changes induced by denaturants. An excited state pK(a)* of 4.9 was identified for **quinacrine**, but the protonation was suppressed in the mustard **conjugate** of serum albumin until the N F transition took place. The properties of the mustard **conjugates** are discussed in terms of potential uses and compared with properties of other types of fluorescent **conjugates**.

L16 ANSWER 20 OF 20 MEDLINE DUPLICATE 10
74045591 Document Number: 74045591. PubMed ID: 4128136. Staining of human metaphase chromosomes with fluorescent **conjugates** of polylysine.
Latt S A; Gerald P S. EXPERIMENTAL CELL RESEARCH, (1973 Oct) 81 (2) 401-6.
Journal code: EPB; 0373226. ISSN: 0014-4827. Pub. country: United States.
Language: English.

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